

DETAILED ACTION

Response to Amendments

Applicant's amendments filed 4/29/11 to claims 1, 4-7, and 15 have been entered. Claims 2 and 3 have been canceled. Claims 1, 4-9, and 11-15 remain pending in the current application. References not included with this Office action can be found in a prior action. Any rejections of record not particularly addressed below are withdrawn in light of the claim amendments and applicant's comments.

Election/Restrictions

Applicant's election of the species "mammalian cells" and "a polypeptide" in the reply filed on 7/23/10 (and reiterated in the 10/20/10 reply) is still in effect over the claims.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1, 4-9, and 11-15 remain rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 includes the functional limitations "wherein no more than 5% of the animal cells in the culture form aggregates of at least 5 cells during the continuous perfusion culturing" and "resulting in an outflow of liquid having a lower animal cell density than the cell culture," which is confusing because it is not clear whether these effect is an inherent result of some process steps (presumably, culture, addition of

Art Unit: 1653

media, and/or circulation over a filter module) or whether some additional step is required to achieve this result. Applicant alleges that the claim is clear. (Reply at 8, part (c).) The examiner disagrees. Applicant has not clearly admitted on the record that all methods that include adding cell culture medium and circulating the resulting culture through a filter module with alternating tangential flow (ATF) inherently yield the recited outcome. Applicant has also not clearly stated that no additional steps or conditions are necessary to yield this outcome. It is not clear which methods are included in the claim's scope and which are not. Clarification is still required.

Claim 1 also refers to "lower animal cell density," which the examiner queried in the 1/5/11 Office action. The examiner requested clarification on whether "lower animal cell density" refers to the number of cells per volume of medium or to cells that are physically lower in density than other cells (e.g., adipocytes float on water, while lipid droplet-free cells do not). Applicant's reply merely alleges that the claim language is clear. (Reply at 8, part (d).) These statements do not address the two reasonable interpretations of the phrase "cell density" as set forth by the examiner. Clarification is still required.

Because claims 4-9 and 11-15 depend from indefinite claim 1 and do not clarify these points of confusion, they must also be rejected under 35 U.S.C. 112, second paragraph.

Claim 4 requires that additional media be placed into the culture vessel "to compensate for the biomass removal," but the nature of this compensation is unclear. Applicant should clarify whether the compensation is merely one of mass or volume or

Art Unit: 1653

whether the added medium carries out some function that the culture lost when the biomass was removed. Clarification is required.

Claims 8 and 9, like claim 1, recite end results of a method without making clear whether it is the inherent effect of the method steps in claim 1 and only those steps, or whether it is achieved only by carrying out additional steps or under certain conditions. Clarification is required. Applicant alleges that these are "the additional limitations imposed by the claim" and that the claims are clear. (Reply at 10-11, part (k).)

Applicant's comments suggest that these limitations are intended to limit the method of claim 1 to only those embodiments in which 90% of the cells survive and in which less than 4% of the cells form 5-cell aggregates. As discussed above, however, these functional limitations do not provide any specific guidance about which conditions, parameters, or steps are necessary to give rise to these results. Clarification is required.

Claim Rejections - 35 USC § 103

The language of a claim must make it clear what subject matter the claim encompasses to adequately delineate its "metes and bounds." See, e.g., *In re Hammack*, 427 F.2d. 1378, 1382, 166 USPQ 204, 208 (CCPA 1970). The courts have also indicated that before claimed subject matter can properly be compared to the prior art, it is essential to know what the claims do in fact cover. See, e.g., *In re Steele*, 305 F.2d. 859, 134 USPQ 292 (CCPA 1962). In this case, the claims are nearly so indefinite as to preclude a substantive search by the examiner. However, in the interest of compact prosecution, the examiner has made an earnest effort to examine applicants'

Art Unit: 1653

invention as defined by the claims. The fact that the examiner has attempted to interpret the claims for art rejection purposes does not obviate applicants' obligation to particularly point out and to distinctly claim the invention.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1, 4-9 and 11-15 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Kyung et al. (1994, *Cytotechnology* 14: 183-90; reference 8 on 7/23/10 IDS) taken in view of Shevitz (2003, U.S. Patent 6,544,424; on 11/13/07 IDS), and Furey (2000, *Genetic Engineering News* 20: 52-53; on 11/13/07 IDS).

Kyung teaches culturing human embryonic kidney epithelial cells ("293 cells") in continuous perfusion culture in a bioreactor until the cells reach a density of approximately 100×10^6 cells/mL. Page 184 under "Cell culture"; Figure 2. Kyung's

Art Unit: 1653

bioreactor employs two peristaltic pumps and five ports to remove spent media (“biomass”) and to provide fresh media at a controlled rate. Pages 184-85, under “Bioreactor instrumentation.” During the culturing, Kyung’s 293 cells produce protein C. Figure 2. Kyung teaches optimizing the calcium concentration of the medium in order to reduce cell aggregates. Page 188, first full paragraph. Kyung’s culturing method yields viability greater than 95%. Page 188, first full paragraph.

Kyung does not teach a bioreactor that provides alternating tangential flow. Kyung does not specifically point out the number or size of cell aggregates that result from the method.

Shevitz teaches a bioreactor comprising hollow fibers **18**, two pumps **24** and **46**, and a filter compartment **4** that provide an alternating tangential flow (“ATF”) that continuously filters fluids by flowing the media first in one direction, then in another. Column 3, line 42, through column 4, line 11; Figure 1; columns 6-8. Shevitz’s bioreactor permits the culture to achieve high cell concentrations and to reach a steady state. Column 3, lines 18-28; column 14, lines 44-47. Shevitz’s bioreactor eliminates large cell aggregates from the culture in two ways: by preventing their formation with the two-way flow (column 3, lines 37-41; column 9, lines 64-66; column 15, lines 7-12) and by filtering out the ones that do form (column 14, line 64, through column 15, line 7). Shevitz notes that the ATF bioreactor is an improvement over standard batch culture because the ATF perfusion system yields cell concentrations “from about 1 to about 20 times that achieved in a batch process.” (Column 14, lines 44-46.)

Furey teaches culturing cells in Shevitz's ATF bioreactor. Figure 3; page 53, under "ATF system." Furey teaches that cells so cultured grow and produce proteins. Figure 3, triangle and diamond symbols. Furey teaches that the ATF bioreactor can be perfused at a steady rate. Figure 3, "x" symbols. Furey recognizes perfusion culture, and specifically the ATF bioreactor, is useful for yielding cultures with high viability and high cell concentration. Page 52, column 2; page 53, column 3.

A person of ordinary skill in the art would have had a reasonable expectation of success in carrying out Kyung's 293 cell culturing in Shevitz's ATF bioreactor because both Kyung's and Shevitz's bioreactors permit long term, continuous perfusion culture. Furthermore, Shevitz specifically contemplated culturing cells in the bioreactor, and Furey demonstrated that the ATF bioreactor can support high-density, highly viable mammalian cell culture. The skilled artisan would have been motivated to substitute Shevitz's ATF bioreactor for Kyung's because Shevitz's bioreactor prevents the formation of cell aggregates, which Kyung recognized as being undesirable in suspension culture of mammalian cells. Furthermore, Kyung noted a decrease in cell viability after several weeks (page 188, column 1); therefore, the skilled artisan would have been motivated to select Shevitz's ATF bioreactor because Furey teaches that the ATF bioreactor can yield high concentrations of viable cells for an extended period.

The skilled artisan would have had a further reasonable expectation of confining cell aggregates to less than 5% of the total culture and fewer than five cells per aggregate because Kyung teaches that aggregate formation may be controlled by optimizing the contents of the culture medium and Shevitz's ATF bioreactor is

Art Unit: 1653

specifically designed to eliminate aggregates and to inhibit their formation. The skilled artisan would have been motivated to eliminate aggregates because Kyung recognized that they are undesirable in mammalian cell suspension culture.

The selection of the rate of addition of fresh medium and the amount of spent medium to remove would have constituted routine optimization at the time of the invention, the skilled artisan recognizing Kyung's teaching that the amounts fed and withdrawn may be modulated by changing the pump settings and Shevitz's inclusion of numerous controls that optimize culture conditions (e.g., the valves **10**, **19**, **21**, and **23** see column 6, lines 64-66, e.g.; a controller, see column 8, lines 27-32; see also claim 27, e.g.).

It would therefore have been obvious to a person of ordinary skill in the art at the time the invention was made to substitute Shevitz's ATF bioreactor for Kyung's in order to facilitate long-term perfusion culture; to prevent aggregate formation; and to control the addition and removal of medium, especially given Furey's working example in which mammalian cells were successfully cultured in Shevitz's ATF bioreactor.

Therefore, the invention as a whole would have been prima facie obvious to a person of ordinary skill at the time the invention was made.

Regarding Kyung, applicant alleges that a skilled artisan would have had no reasonable expectation of success in carrying out the claimed method with the required results. (Reply at 12, part (A).) These arguments have been fully considered, but they are not persuasive of error. One cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re*

Art Unit: 1653

Keller, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). The examiner agrees that Kyung alone does not provide sufficient teachings to render the invention obvious; that is the reason for this rejection being made under section 103 over Kyung, Shevitz, and Furey.

Regarding Shevitz, applicant alleges that the “aggregates” avoided in that method are not cell aggregates, but rather “particulate aggregates.” (Reply at 13-15.) Applicant refers to various teachings within Shevitz in taking the position that Shevitz does not mention cell aggregates and, therefore, does not pertain to them. (Reply at 13-15.) The examiner disagrees with applicant’s interpretation of Shevitz on two levels.

As an initial matter, Shevitz clearly and explicitly states that the method and apparatus in that patent are for use in biological culturing methods. “Such a system has applications in perfusion of cultured animal cells as well as other varied filtration applications.” (Column 6, lines 21-23; see also column 2, lines 18-27; column 3, lines 42-53; column 13, lines 18-25 (describing biological fluids as a preferred embodiment); column 14, lines 44-46; and claim 11.) Applicant’s interpretation of Shevitz gives the impression that Shevitz was not concerned with cell aggregates at all, but this is clearly not the case.

Applicant reads Shevitz's lists as excluding aggregates of cells from its disclosure. The examiner disagrees with this reading of Shevitz. For example, at page 14, applicant interprets “aggregates” in the phrase “dead cells, cell debris, aggregates or other constituents of the fluid” as referring to “non-cell aggregates” because they are distinguished from “dead cells.” An equally reasonable interpretation, however, is that

Art Unit: 1653

“aggregates” is distinguished from “dead cells” because “aggregates” may include “cell aggregates,” i.e., aggregates containing live cells. Aggregates of live cells were a problem recognized in the art (see, e.g., Kyung at 188, column 1). There is no clear evidentiary reason to select applicants’ interpretation over the examiner’s, especially given the fact that a skilled artisan considering Shevitz’s ATF bioreactor would have known about the possibility of live-cell aggregate formation (see Kyung). The fact that Shevitz did not recite the word “cell” before “aggregate” in the portions applicants highlight is not dispositive, especially given the explicitly stated utility of Shevitz’s ATF bioreactor in culturing live cells.

Finally, even if Shevitz’s ATF bioreactor were not “specifically designed to eliminate cell aggregates and to inhibit their formation,” which the examiner does not concede, the reference would still be applicable and highly relevant. The fact that applicant has recognized another advantage which would flow naturally from following the suggestion of the prior art cannot be the basis for patentability when the differences would otherwise be obvious. See *Ex parte Obiaya*, 227 USPQ 58, 60 (Bd. Pat. App. & Inter. 1985). The issue is not whether Shevitz practiced the invention with cells and observed less aggregation, but rather whether the skilled artisan would have known that Shevitz’s ATF bioreactor actually yields a culture with high numbers of large aggregates and/or low viability. Shevitz explicitly teaches, “the cell concentration achieved in the [ATF] perfusion according to the invention is from about 1 to about 20 times that achieved in a batch process.” (Column 14, lines 44-46.) The teachings of Furey are further instructive, because Furey explicitly noted the usefulness of the ATF bioreactor

Art Unit: 1653

for maintaining high numbers of viable cells over extended periods. (Page 53.) Finally, Shevitz's entire bioreactor is designed to prevent the formation of aggregates (i.e., aggregates in general) and to remove them when they do form. Shevitz teaches that aggregation is avoided in the ATF bioreactor, and Shevitz teaches that the ATF bioreactor is designed for culturing biological cells. Shevitz teaches that conventional perfusion devices were known to clog with aggregates over time. (Column 2, lines 54-56.) Taken together, the clear teaching of Shevitz is that aggregates of all types (including both cell aggregates and aggregates of debris and dead cells) are inhibited and removed by the flow pattern in the ATF system. There is no evidence that Shevitz's ATF system affects only those aggregates that do not contain 5 or more cells. The skilled artisan, considering Shevitz as a whole and in light of Furey, would have had a reasonable expectation that culturing cells and media in the ATF bioreactor of Shevitz would inhibit the formation of all aggregates and remove those that do form. When the references are considered as a whole and in light of the common sense of the skilled artisan, the claimed invention is obvious.

Applicant's evaluation of the combination of references is also unavailing. (Reply at 15, last paragraph.) Applicant alleges that Kyung's method does not yield a sufficiently viable culture to meet the claim limitations, specifically that at 400 hours of culturing, the culture contains only 7.9×10^7 viable cells, not the "at least 8.0×10^7 " cells required by the claims (the claim term " 80×10^6 " is equivalent to 8.0×10^7). There are two issues here. First, the question is not what Kyung alone teaches, but rather what the cited references, taken together, would have suggested to the skilled artisans.

Art Unit: 1653

Assuming applicant's calculations are accurate (the examiner can find no clear error), then after 400 hours in Kyung's perfusion system, the culture contains 98.8% of the minimum number of cells required by the claims. However, Shevitz teaches that the ATF bioreactor is an improvement over the prior art perfusers, and Furey teaches that the ATF bioreactor can maintain high cell density after extended culture times. The skilled artisan, considering all of the teachings, would reasonably conclude that the ATF bioreactor would likely improve the cell concentration relative to that in Kyung's older method.

Even if one were to disagree that it is unreasonable to expect a 1.2% increase in cell concentration in an apparatus that is clearly defined as an improvement, applicant has misstated the teachings of Kyung. It is true that at 400 hours, the viability of the cells is 85%. (Page 188, column 1.) However, through 280 hours, the culture had viability "greater than 95%." Therefore, the viability of the cells in Kyung's bioreactor decreased between day 281 and day 400 – the exact problem that Shevitz and Furey's ATF bioreactor solves. Given Shevitz and Furey's teachings of improvement over prior-art perfusers, the skilled artisan would have had a reasonable expectation that the ATF bioreactor would yield at least 1.2% more cells at some point than Kyung's did at 400 days.

And even if one were to consider it unreasonable to think that extremely high cell viability would be maintained in Shevitz and Furey's ATF bioreactor, again, the skilled artisan would have considered all of the teachings in Kyung and concluded that in order to get more cells, all that would be required is to culture for a few days more. Figure 2 of

Art Unit: 1653

Kyung clearly demonstrates that overall cell concentration in that bioreactor rose steadily throughout the 400 days of culturing and did not plateau at any time. Increasing the density from 79,000,000 cells/mL to 80,000,000 cells/mL is not an extreme increase, and the skilled artisan would not have considered that extrapolation to be unreasonable. Applicant has provided no evidence that after 400 days, cell viability dropped to 0% (or by any particular degree). Given the evidence in Figure 2, the skilled artisan would reasonably have predicted that the cell concentration would rise over time and, if more cells were necessary, would have continued the culture beyond 400 days.

Applicant concludes by alleging that the claimed invention yields the unexpected result that cell aggregates are disaggregated. (Reply at 16.) As an initial matter, these statements are merely the argument of counsel and are unsupported by evidence or declarations of those skilled in the art. Counsel's arguments cannot take the place of objective evidence. *In re Langer*, 183 USPQ 288 (CCPA 1974). M.P.E.P. § 716.01(c) explicitly directs that allegations of unexpected results must be supported by an appropriate affidavit or declaration.

In any case, unexpected results must be truly unexpected and unobvious, and they must be of practical and statistical significance. M.P.E.P. § 716.02(b). Applicant alleges without basis that "low shear conditions typically do not lead to disaggregation of cells" and that cell aggregation is "particularly troublesome" if enough large aggregates form. Without at least an affidavit of one skilled in the art, these assertions are mere attorney conjecture. Applicant has also provided no evidence or affidavit regarding skilled artisans' expectations at the time of filing, and there is no comparative evidence

Art Unit: 1653

on the record, much less data that demonstrates both a practically and statistically significant result when applicants' method is used relative to that of the prior art. The arguments are merely bare statements that the claimed invention is an improvement, and this is inadequate to meet the requirement to overcome the obviousness rejection.

No claims are allowed. No claims are free of the art.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Lora E. Barnhart whose telephone number is (571)272-1928. The examiner can normally be reached on Monday-Thursday, 9:00am - 5:30pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sue X. Liu can be reached on 571-272-5539. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Art Unit: 1653

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/Lora E Barnhart/
Primary Examiner, Art Unit 1653